

REMARKS

Claims 1-3, 5, 9-33, 36-38, 41-44 and 60-63, 65, and 67-70 are pending in the application, with claims 1, 60, 63 and 65 being independent, claim 64 being cancelled, and claims 12, 13, 16-32 and 65-66 being withdrawn. New claims 67-70 have been added. Care has been taken to avoid the introduction of new matter.

New independent claim 67 is directed to a preferred, substantially linear, block co-polymer comprising at least one hydrophobic polymer covalently bound at a proximal end to a surface, and at least one hydrophilic polymer covalently bound to the hydrophobic block, wherein a distal end of the hydrophilic block contains a terminal reactive group which excludes a carboxyl and which reactive group is suitable for forming a covalent bond with a surface modifying substance in aqueous solution or suspension. Support for this claim can be found e.g., on page 15, line 28 to page 17, line 2.

New claim 68 is directed to the same block co-polymer wherein the hydrophobic block comprises one or more polymers containing polylactic acid, polyglycolic acid, or a mixture of lactic acid and glycolic acid moieties, and the hydrophilic block comprises a modified polyethylene glycol having an amino group and a reactive group which excludes a carboxyl suitable and which is suitable for forming a covalent bond at a distal terminus with a surface modifying substance. Support for this claim can be found at page 15, line 28 to page 17, line 2 and Examples 1 and 2.

New claim 69 further narrows the claimed co-polymer to specify that the hydrophobic block comprises polylactic acid wherein the hydrophilic block comprises poly (ethanolamine) (PEG-NH₂). Support for this claim can be found, also, at page 15, line 28 to page 17, line 2 and Examples 1 and 2.

New claim 70 further specifies the co-polymer of claim 69, by adding that the hydrophobic block has a molecular weight of 100-100,000 Da and that the hydrophilic block contains from a single ethanolamine to a poly(ethanolamine) having a molecular weight of about 10,000 Da. Support for this claim, again, can be found at, e.g., page 21, lines 1, 16-18 and 24-27, and page 22, lines 10-11.

Rejection pursuant to 35 U.S.C. §102(e)

Claims 1-3, 5, 11, 14, 15 and 33 were again rejected as allegedly being anticipated pursuant to 35 U.S.C. §102(e) by Hirose et al. (US 6254890; “Hirose” or “the ‘890 patent”). Applicants respectfully traverse this rejection for the following reasons.

A patent claim is not anticipated pursuant to 35 U.S.C. §102 unless a single prior art reference contains each and every limitation of the claim, adequately describes the invention, and teaches a person of skill in the art to make and use the invention without undue experimentation. See e.g., *In re Paulsen*, 30 F.3d 1475, 31 USPQ 2d 1671 (Fed. Cir 1994). Specifically, 35 U.S.C. §102(e) is a codification of Justice Holmes’ opinion in *Alexander Milburn Co. v. Davis-Bournonville Co.*, 270 U.S. 390 (1926)(hereinafter *Milburn*), in which the United States Supreme Court held that a patent issued to the senior party after (but filed before) the filing date of the junior party’s application may constitute prior art against the application because, having given a “complete and adequate description” of the junior party’s invention, the senior party “had done all that he could to make his description public. He had taken steps that would make it public as soon as the Patent Office did its work. . . .” *Milburn*, 270 U.S. at 399 (emphasis added). Even after the enactment of 35 U.S.C. §102(e), Justice Holmes’ opinion in *Milburn* has continued to define how an earlier filed, later published patent can constitute prior art under this section.

Thus, in the case of *In re Wertheim and Mishkin*, 209 USPQ 554 (CCPA 1981)(hereinafter *Wertheim*), decided after enactment of the Patent Act of 1952, the Court of

Customs and Patent Appeals held that “if a patent [on the accused invention] could not theoretically have issued the day the [senior party’s] application was filed, it is not entitled to be used against another . . .” *Id.* at 564 (emphasis in original). Therefore, “the determinative question is whether the invention claimed in the senior party’s publication finds a supporting disclosure in compliance with §112” and “[w]ithout such support, the invention, and its accompanying disclosure, cannot be regard[ed] as prior art....” *Id.* (emphasis in original).

In the Advisory Action mailed June 5, 2009 the Examiner indicated that “reliance on the Milburn opinion is confusion, as that opinion was issued before the Patent Act of 1952 and dealt with different statutes than are at issue here.” See Advisory Action, page 2. Respectfully, however, Applicants disagree that *Milburn* is inapposite to the present §102(e) rejection; as stated by Judge Rich, one of the authors of the Patent Act of 1952, “Section 102(e) . . . was a codification of the rule of *Alexander Milburn Co. v. Davis-Bournonville Co.*, 270 U.S. 390, 46 S.Ct. 324, 70 L.Ed. 651 (1926),” and both the rule and the rationale of *Milburn* survived the enactment of the Patent Act. *In re Klesper*, 397 F.2d 882, 885 (CCPA 1968)(Rich, J.) Therefore, §102(e), interpreted as it must be through the lens of *Milburn* and the subsequent case law, including *In re Wertheim*, described above, requires that a prior filed, later-issued patent (or later-published patent application) contain a disclosure having sufficient detail (enabling disclosure, adequate description) that an invention could have been patented on the filing date of the patent application, “but for” Patent Office delay.

The Final Office Action references the figure shown on page 8 of the September 4, 2008 Office Action (drawn by the Examiner) to illustrate what it alleges to be disclosed by Hirose et al. in Example 4 of the ‘890 patent. However, Example 4 actually states, with emphasis added, as follows:

Method for Attaching Surface-Masking and/or Targeting Moieties

Surface masking characteristics are provided by PEG on the nanospheres by using various PEG-PLA and PLGA mixtures in the initial polymer solution. Non-covalent attachment of targeting moieties is achieved by incubating biotin-PEG-PLA: PLGA nanospheres with excess streptavidin or avidin, in turn, incubating the avidinylated spheres with biotin-ligand. **Covalent attachment methods use activated esters (N-hydroxysuccinimidyl esters) on PEG-PLA with which amine groups from desirable ligands can be reacted.**

Since the presently claimed block copolymers are, by definition, covalently bonded molecules, logically the Office Action must be relying on the last sentence of Example 4 for the rejection of the present claims. However, this sentence (“Covalent attachment methods use activated esters (N-hydroxysuccinimidyl esters) on PEG-PLA with which amine groups from desirable ligands can be reacted”) gives absolutely no written description or enablement of the specific invention of any of the present claims e.g., present claim 1. Nor does Hirose provide sufficient support as required by §112 to meet Justice Holmes’ requirement that Hirose have “done all he [they] could do” to disclose the presently claimed invention.

Respectfully, the quoted sentence does not even provide enablement or written-description support for the chemical structure presented on page 8 of the last Office Action. Hirose, while using the term “PEG-PLA,” does not provide an unambiguous definition of the chemical structure intended by this term. Specifically, Applicants must disagree with the Advisory Action’s statement that “PEG-PLA is a well known term of art, referring to an AB block copolymer of polyethylene glycol and polylactic acid,” such that the term requires no further description. To this point, Applicants introduce as evidence Appendix A in the form of an exemplary abstract (Liggins et al., Characterization Of PEG-PLA Liquid Triblock Copolymers Useful For Controlled Delivery Of Paclitaxel (May 8, 2006)) from the American Association of Pharmaceutical Scientists website (apparently a meeting poster presentation), which shows that “PEG-PLA” means ABA triblock co-polymers, rather than AB diblock co-polymers, to certain persons of skill in the art.

See http://www.aapsi.org/abstracts/AM_2006/AAPS2006-002396.pdf. Thus, the term

PEG-PLA is not unambiguous, and the disclosure of the '890 patent simply fails to provide the required unambiguous description to anticipate or render obvious any of the present claims.

The Examiner's chemical structure on page 8 postulates that the amine moiety of the '890 patent is linked to the PEG portion of the PEG-PLA, but Hirose does not state this. Additionally, it is not clear how this entity is attached to the nanosphere, whether the entity has a branched or linear structure, what the stoichiometry of the PEG and PLA moieties is, the molecular weight of the structure, whether there is a single or are multiple attachment points for each PEG-PLA unit to the surface, and so forth. Under *Milburn* in order to anticipate, a §102(e) reference must contain a **complete and adequate description** of the invention it purports to disclose; thus, the disclosure of Hirose is clearly inadequate for this purpose. Therefore Applicants respectfully contend that Hirose is not prior art to the present claims, and that claims 1-3, 5, 11, 14, 15, and 33 are not anticipated by Hirose. For these reasons, Applicants respectfully request reconsideration and withdrawal of the outstanding rejection of the claims.

Finally, Hirose completely lacks any intimation of a composition as claimed, e.g., in claim 62 which specifies the block copolymer of Claim 61 wherein the hydrophilic polymer b) is poly(ethylene glycol) amine (PEG-NH-d2), or in new claims 68-70. These claims contain limitations simply not found in Hirose. For example, claim 67 requires that the polymer be substantially linear, and claim 68 states the hydrophilic block comprises a modified polyethylene glycol having an amino group wherein the co-polymer has a reactive group other than a carboxyl suitable for forming a covalent bond at a distal terminus with a surface modifying substance. Additionally, claim 69 states that the hydrophobic block comprises polylactic acid wherein the hydrophilic block comprises poly (ethanolamine) (PEG-NH₂), and claim 70 states that the hydrophobic group of the co-polymer has a molecular weight of 100-100,000 Da and that the hydrophilic block contains from a single ethanolamine to a poly(ethanolamine) having a molecular weight of about 10,000 Da. None of these limitations can be found, either expressly or inherently, in the '890 patent.

Rejection pursuant to 35 U.S.C. §103

Similarly, claims 1-3, 5, 9-15, 33, 36-38 and 41-44 were rejected as allegedly obvious over Hirosue in view of Domb. Applicants respectfully traverse this rejection for the reasons provided above, and the additional reasons given below.

As stated above, Hirosue is respectfully submitted not to be prior art to instant claims 1-3, 5, 9-15, 33, 36-38 and 41-44 pursuant to e.g., *Alexander Milburn Co. v. Davis-Bournonville Co.*, 270 U.S. 390 (1926)(hereinafter *Milburn*), and *In re Wertheim and Mishkin*, 209 USPQ 554 (CCPA 1981)(hereinafter *Wertheim*). Applicants note that *Wertheim* concerned a §102(e)/103 obviousness rejection in which the priority date of the reference used by the U.S.P.T.O. as §102(e)/103 prior art was at issue. The *Wertheim* court held that, with regard to the subject matter used against the disclosure, “if a patent **could not** theoretically have issued the day the application was filed, it [the application] is not entitled to be used against another” *Wertheim*, 209 U.S.P.Q. at 564 (emphasis in original). A patent cannot issue on an invention that lacks an enabling disclosure and an adequate written description. For the reasons given above, Example 4 of Hirosue does not constitute an enabling disclosure or an adequate written description of an invention. Therefore, Hirosue is not prior art against any of the present claims, either alone or in combination with Domb.

However, even if Hirosue were prior art, the relevant disclosure, as shown above, comprises a single sentence containing an ambiguous disclosure of covalent PEG-PLA Compositions. Hirosue does not discuss linear polymers of modified PEGs, such as ethanolamine, as are claimed in e.g., claims 62 or 68-70.

Domb is cited solely for providing the molecular weights of PEG-PLA polymers. Thus, Domb, taken alone, does not render the presently pending claims obvious. Hirosue and Dob, if combined completely fail to suggest all the limitations of the present claims.

Applicants: GÖPFERICH, Achim et al.
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Conclusion

For the reasons presented above, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §102 and §103.

In view of the above, the Examiner is requested to consider the application now to be in condition for allowance, and an early indication of same is requested. The Examiner is invited to contact the undersigned with any questions.

The Commissioner is hereby authorized to charge any needed fees to Deposit Account 50-1600.

Respectfully submitted,



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APPENDIX A

Characterization of PEG-PLA liquid triblock copolymers useful for controlled delivery of paclitaxel.

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Purpose. To characterize triblock copolymer excipients useful in preparing injectable formulations of paclitaxel. Methods. Copolymers of PEG and various polyesters were synthesized by ring opening polymerization. Copolymer viscosity, water solubility (measured gravimetrically) and solubility parameter, estimated from solubility in solvents with hydrogen bonding solubility parameter (δ_H) ranging from 0 (toluene) to 42 (water), were determined. Polymer structure characterized by its highest δ_H solvent (Max δ_H) was correlated to formulation performance, measured in terms of drug release via partitioning from the copolymer into aqueous media. Paclitaxel concentrations in media were quantified by C18 HPLC. Results. Copolymers having a center block of PEG MW (A) between 200 and 20k g/mol and terminal blocks of PLA of combined MW (B) between 100 and 9k g/mol were synthesized. Polymer viscosity identified the operability range of 200-900 g/mol for both A and B, where polymers were liquid and injectable. Water solubility, Max δ_H and viscosity all varied with A and B. Within the operable range, effects were described by response surface mapping to obtain the simplest significant model (see Table, $p < 0.01$). Release due to partitioning of paclitaxel from the water insoluble copolymer into media over 72 hours (72h Rel.) ranged from 2 to 100% of total loading depending on polymer structure. A best fit empirical relationship described the drug depot behavior in polymers: $\log(72h \text{ Rel.}) = 5.9 \cdot 10^{-4} \cdot \text{Max } \delta_H - 0.44$, $R^2 = 0.93$. The relationship was valid for all PEG-PLA copolymers and was predictive for PEG copolymers made with PLGA and PCL. Conclusions. PEG-PLA triblock copolymers have well-defined physical properties which are dependent on both PEG and PLA block lengths. The solubility parameter property of the polymers was related to their action as a depot for paclitaxel in release studies. This relationship was predictive for similar behavior in copolymers made with other polyesters.

Response surface mapped model equation A = PEG MW, B = PLA MW	Adj. R ²	P
Max $\delta_H = 58.3 - 0.026A - 0.095B + 1.53AB + 5.78B^2 - 1.18AB^2$	0.87	<0.0001
Water insoluble fraction = $-0.099 + 1.88A + 6.72B - 1.41AB + 9.10B^2$	0.93	<0.0001
Viscosity = $160 + 0.589A - 1.34B + 1.75AB - 2.76A^2 + 2.29 + 3.05A^2B - 4.30AB^2 + 1.05A^3 - 4.43B^3$	0.99	<0.0057